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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/992,443
Filing Date	November 16, 2001
First Named Inventor	Levitsky et al.
Group Art Unit	1632
Examiner Name	Li, Q. J.
Total Number of Pages in This Submission: 3	Attorney Docket Number: P2133CON

ENCLOSURES *(check all that apply)*

- [X] Fee Transmittal Form
  - [X] Fee Attached
- [ ] Amendment / Response
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [X] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Revocation of Former Power of Attorney and New Power of Attorney
- [ ] Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [X] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Additional Enclosure(s) *(please identify below)*:
  - **Transmittal of Appellant's Appeal Brief**
  - **Appendix**
  - **Postcard**

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Carol Larcher, Reg. No. 35,243 Gardner Carton & Douglas LLP
Signature	Carol Larcher
Date	August 20, 2004

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class mail in an envelope addressed to: Mail Stop Appeal Brief - -Patents, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 on this date August 20, 2004.

Typed or printed name	Angelica Diaz		
Signature	Angelica Diaz	Date	August 20, 2004

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CH02/ 22324261.1

PATENT
Attorney Docket No. 1030/P2133-US 443
Client Reference No. DM-3341; JHU 101.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Levitsky et al.

Art Unit: 1632

Application No. 09/992,443

Examiner: Li, Q. J.

Filed: November 16, 2001

For: A UNIVERSAL IMMUNOMODULATORY CYTOKINE-EXPRESSING BYSTANDER CELL LINE AND RELATED COMPOSITIONS AND METHODS OF MANUFACTURE AND USE

TRANSMITTAL OF
APPELLANTS' APPEAL BRIEF

Mail Stop Appeal Brief — Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In accordance with 37 CFR 1.192, appellants hereby submit Appellants' Brief on Appeal in triplicate.

The items checked below are appropriate:

1. Status of Appellants

This application is on behalf of ☐ other than a small entity or ☒ a small entity.

The verified statement ☐ is attached or ☐ was filed on .

2. Fee for Filing Brief on Appeal

Pursuant to 37 CFR 1.17(e), the fee for filing the Brief on Appeal is for: ☐ other than a small entity or ☒ a small entity.

Brief Fee Due $165.00

3. Oral Hearing

☐ Appellants request an oral hearing in accordance with 37 CFR 1.194.

4. Extension of Time

☒ Appellants petition for a one-month extension of time under 37 CFR 1.136, the fee for which is $55.00. Appellants believe that no further extension of time is required. If, however, an additional extension is required, please consider this a conditional petition therefor and charge Account No. 07-0181 accordingly.

☐ Appellants believe that no extension of time is required. However, this conditional petition is being made to provide for the possibility that appellants have inadvertently overlooked the need for a petition and fee for extension of time.

Extension fee due with this request: $55.00

5. Total Fee Due

The total fee due is:

Brief on Appeal Fee	$165.00
Request for Oral Hearing	$ 0.00
Extension Fee (if any)	$ 55.00

Total Fee Due: $220.00

6. Fee Payment

☒ Attached is a check in the sum of $220.00.
☐ Charge Account No. 07-0181 the sum of $0.00. A duplicate of this transmittal is attached.

7. Fee Deficiency

☒ If any additional fee is required in connection with this communication, charge Account No. 07-0181. A duplicate copy of this transmittal is attached.

Carol Larcher, Reg. No. 35,243
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Date: August 20, 2004

CH02/ 22324226.1

PATENT
Attorney Docket No. 1030/P2133-US 443
Client Reference No. DM-3341; JHU 101.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Levitsky et al.

Art Unit: 1632

Application No. 09/992,443

Examiner: Li, Q. J.

Filed: November 16, 2001

For: A UNIVERSAL IMMUNOMODULATORY CYTOKINE-EXPRESSING BYSTANDER CELL LINE AND RELATED COMPOSITIONS AND METHODS OF MANUFACTURE AND USE

APPELLANTS' BRIEF ON APPEAL

Mail Stop Appeal Brief -- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Appellants hereby appeal to the Board of Patent Appeals and Interferences from the decision of the Examiner finally rejecting claims 1-14, 17-28, 40-47 and 50-53 in the final Office Action dated December 17, 2003, as further evidenced by the Advisory Action dated May 3, 2004.

Real Parties In Interest

The real parties in interest are the assignee, Johns Hopkins University School of Medicine, and the licensee, Cell Genesys.

Related Appeals and Interferences

To the best of the knowledge of Appellants' representative, there are no pending appeals and interferences, which will directly affect or be affected by or have a bearing on the Board's decision in this appeal.

Status of Claims

Claims 1-14, 17-28, 40-47 and 50-53 are currently pending and are hereby appealed. Claims 15, 16, 29-39, 48 and 49 have been canceled previously and are not the subject of this appeal.

Status of Amendments

Claim 2 was amended after final rejection to address matters of form. The amendment to claim 2 was entered by the Examiner.

Summary of Invention

The invention is directed to a universal bystander human cell line, which (i) is a human cell line, (ii) naturally lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens, and (iii) is modified by introduction of a nucleic acid molecule comprising a nucleic acid sequence encoding granulocyte macrophage-colony stimulating factor (GM-CSF) operably linked to a promoter (specification at, for

example, page 5, lines 1-10; page 6, line 28, through page 7, line 2; page 8, line 1, through page 12, line 2). The universal bystander cell line expresses about 500 ng or greater GM-CSF/10^6 cells/24 hours (specification at, for example, page 5, lines 10-12; page 12, lines 3-7). The invention is also directed to a composition comprising the universal bystander cell line and a cancer antigen (specification at, for example, page 5, lines 26-27; page 12, line 17, through page 13, line 18; Example 2 (page 19, line 26, through page 20, line 16)).

A method of making a universal GM-CSF-expressing bystander cell line is further provided (specification at, for example, page 5, lines 27-29). The method comprises (i) obtaining a human cell line that lacks MHC-I antigens and MHC-II antigens, (ii) modifying the human cell line by introducing into the human cell line a nucleic acid molecule comprising a nucleic acid sequence encoding GM-CSF operably linked to a promoter and a nucleic acid sequence encoding a selectable marker operably linked to a promoter, and (iii) using the selectable marker to isolate cells that produce about 500 ng or greater of said GM-CSF/10^6 cells/24 hours (specification at, for example, page 13, line 19, through page 14, line 28; Example 1 (page 18, line 8, through page 19, line 24)).

A method of stimulating an immune response to a cancer in a human patient is still further provided (specification at, for example, page 5, lines 29-30; page 14, line 29, through page 18, line 2; Example 2 (page 19, line 26, through page 20, line 16)). The method comprises administering to the patient the above-described composition, in which the cancer antigen is an antigen of the cancer, wherein the composition is irradiated. Upon administration of the composition to the human patient, an immune response to the cancer is stimulated.

Issues on Appeal

The issues on appeal are as follows:

(i) whether or not all of the pending claims lack description and enablement under 35 U.S.C. § 112, first paragraph,

(ii) whether or not all of the pending claims are indefinite under 35 U.S.C. § 112, second paragraph,

(iii) whether or not claims 1, 5, 7, 17, 20, 22, 28, 40, 41, 44, 45, 50 and 52 are obvious in view of and, therefore, unpatentable over Dranoff et al. in view of Ferrone et al., as allegedly evidenced by Thomas et al., alone or in further view of Shepard et al. or Polack et al., under 35 U.S.C. § 103(a), and

(iv) whether or not claims 1-14, 17-28, 40-47 and 50-53 are unpatentable over claims 1-21 of U.S. Patent No. 6,464,973 under the judicially created doctrine of obviousness-type double-patenting.

Grouping of Claims

For each ground of rejection, the rejected claims stand or fall together.

Discussion of Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected all of the pending claims under Section 112, first paragraph, as allegedly lacking description and enablement. The Examiner should be reversed for the reasons set forth below.

The Examiner clearly understands that Appellants' use of the term "naturally" to describe the lack of MHC-I and MHC-II antigens on the universal bystander cell line encompasses a cell line that lacks MHC-I and MHC-II antigens due to a naturally occurring mutation, such as a cancerous mutation. However, the Examiner contends that use of the term "naturally" to encompass such a cell line is contrary to the ordinary meaning of the term, citing *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 U.S.P.Q.2d 1029, 1033 (Fed. Cir. 1999).

At issue in *Process Control* was whether a term, recited in two different clauses of a single claim, should be construed to have the same meaning in both clauses. The Federal Circuit found that the claim language was "susceptible to only one meaning," based on "the

language of the claim itself." *Id.* at 1356. According to the Federal Circuit, the claim language was not susceptible to two different constructions. *Id.* The Federal Circuit further found that the written description did not clearly redefine the disputed claim term so as to put a reasonable competitor or one skilled in the art on notice that the patentee intended to give the claim term a meaning contrary to its ordinary meaning. *Id.* at 1357.

Like *Process Control*, the present specification does not redefine the term "naturally" contrary to its ordinary meaning. The specification makes it clear that "naturally" is distinguished from "modified." See, for example, the specification at page 5, lines 3-6, where the universal bystander cell line is described as a human cell line, which either "naturally lacks" MHC-I antigens and MHC-II antigens, or is "modified" so that it lacks MHC-I antigens and MHC-II antigens. What is meant by "modified" is evidenced in the specification at, for example, page 7, lines 12-14, wherein it is stated that cells that lack MHC-I antigens can be achieved by interfering with the expression and/or transport of the α chain, whereas cells that lack MHC-II antigens can be achieved by interfering with the expression and/or transport of the α and β chains. Thus, a cell line that has been modified so that it lacks MHC-I and MHC-II antigens is one that lacks MHC-I and MHC-II antigens due to manipulation by man. In contrast, a cell line that naturally lacks MHC-I and MHC-II antigens is one that lacks MHC-I and MHC-II antigens without manipulation by man, i.e., it never had MHC-I and MHC-II antigens or, as a result of the effects of nature, it came to lack MHC-I and MHC-II antigens. This is supported by the Examiner's reference to a standard English dictionary as evidencing that the term "naturally" means "by nature, inherently," "without a doubt," and "present or produced by nature" (see Office Action dated April 10, 2003, at page 3, third full paragraph) and the Examiner's acknowledgement that "naturally" encompasses cells, which have lost the capacity to express MHC antigens as a result of naturally occurring mutations, as supported by the references previously provided by Appellants (see Office Action dated April 10, 2003, at page 4, first full paragraph).

Furthermore, like *Process Control*, the use of the term "naturally" in the claims is not susceptible to more than one meaning. For the Examiner to characterize the loss of MHC antigen expression due to a cancerous mutation as not "naturally" occurring (see the top of page 5 of the Office Action dated April 10, 2003) is directly contrary to the evidence of record, including the evidence entered into the record by the Examiner, herself, by way of the

Office Action dated April 10, 2003. This is tantamount to saying that mutations, including cancerous mutations, do not occur naturally, and that every person, who has cancer, has cancer because his/her body was modified, or manipulated by man, in some way to cause the cancer. Appellants maintain that this is the only and, hence, ill-founded basis upon which the Examiner can continue to maintain a rejection for lack of written description. The futility of the Examiner's position is even more apparent when she attempts to characterize "naturally" as descriptive of a genus encompassing mutated and "HEALTHY, i.e. not mutated" cells (see Advisory Action, page 2, continuation of 5.).

The Examiner goes on to contend that the specification fails to disclose a universal bystander cell line that naturally lacks MHC-I and MHC-II antigens. The Examiner opines that the only cell known to lack naturally MHC-I and MHC-II antigens is a red blood cell, for which there is no known cell line, and that mutated tumor cell lines, to the extent that they are encompassed by use of the term "naturally," vary widely in cell-surface markers. Based on this premise, the Examiner contends that one can not predictably determine which cell line meets the limitations of the claims.

Appellants respectfully disagree. Appellants teach the K562 cell line, which lacks MHC-I and MHC-II antigens. In addition, Appellants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigens by searching the PubMed database. Appellants have previously pointed out that numerous examples of such cell lines were known in the art prior to February 2, 1998, the date to which the instant application claims priority, including Wang et al. (1993), Ferrone et al., Kageshita et al., and Wang et al. (1996) (see Response to Office Action dated April 10, 2003, at page 5, for example).

In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003), the Federal Circuit clarified its position in *Regents of the Univ. of Calif. v. Eli Lilly &Co.*, 119 F.3d 1559 (Fed. Cir. 1997), regarding functional descriptions of genetic material. In *Amgen*, the Federal Circuit stated that "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." Id. at 1332. The Federal Circuit went on to say that the facts of both *Eli Lilly* and *Enzo Biochem v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002), do not comport with the facts of *Amgen* because "the claim terms at

issue here [referring to *Amgen*] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *Amgen*, 314 F.3d at 1313.

In view of the above, the claim terms directed to cell lines that lack MHC-I and MHC-II, being known in the art, convey sufficient "information concerning [their] identity such that one of ordinary skill in the art could visualize or recognize the identity of the members of the genus." *Id. quoting Eli Lilly*, 119 F.3d at 1567, 1568. Thus, whether or not there is a red blood cell line is of no import. Likewise, the fact that tumor cell lines may vary widely in cell-surface markers also is of no import.

Whether or not a given human cell line naturally lacks MHC-I and MHC-II antigens is readily ascertainable -- either the human cell line expresses MHC-I and/or MHC-II or it does not. In this regard, the instant specification teaches antibodies (see, e.g., Example 1), which can be used to determine MHC antigen expression, or lack thereof, also as taught by the instant specification (see, e.g., Example 1). Therefore, there is no basis for the Examiner to contend that one of ordinary skill in the art cannot determine whether a cell line lacks MHC-I and MHC-II antigens. Furthermore, database searching for such cell lines and routine screening of cell lines, even if on a "large-scale" basis, do not constitute undue experimentation. See, e.g., *In re Wands*, 858 F.2d 731, 736-737 (Fed. Cir. 1988). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.* at 737. The fact that the Examiner found 471 hits upon searching "HLA loss and tumors" does not evidence undue experimentation. In view of the foregoing and in view of the fact that Appellants need not describe that which is known in the art, Appellants submit that the subject matter of the claims is adequately described.

Therefore, statements made by the Examiner, such as "naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material," and "claiming all cell lines having a common trait without defining what means will do is not in compliance with the description requirement," citing *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993), and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CAFC 1997), clearly do not apply to the instant claims. Likewise, the citation to *Amgen Inc. v. Chugai Pharma. Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), for the proposition that "conception of chemical compound requires that inventor be

able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological activity," also does not apply to the instant claims. As discussed above, *Eli Lilly* does not apply to the present case because cell lines lacking MHC-I and MHC-II are known in the art. Similarly, the arguments made above in connection with *Amgen v. Hoechst* apply to *Fiers* and *Amgen v. Chugai*. Since cell lines lacking MHC-I and MHC-II are known in the art, those ordinarily skilled in the art are able to recognize the identity of the members of the genus. Accordingly, the claims are not overly broad, and are not indefinite under 35 U.S.C. § 112, first paragraph.

In the event that the Board is not persuaded by the above arguments, Appellants would be amenable to amending claim 1 as follows:

1. (Currently amended) A major histocompatibility class I (MHC-I) antigen-negative and major histocompatibility class II (MHC-II) antigen-negative universal bystander human cell line, which ÷

~~(i) is a human cell line,~~

~~(ii) naturally lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens, and~~

~~(iii) is~~ has been modified by introduction of a nucleic acid molecule comprising a nucleic acid sequence encoding granulocyte macrophage-colony stimulating factor (GM-CSF) operably linked to a promoter,

wherein said universal bystander cell line expresses about 500 ng or greater GM-CSF/10^6 cells/24 hours.

With regard to enablement, the Examiner contends that the specification fails to disclose another species of a cell line lacking MHC-I and MHC-II antigens in addition to the K562 cell line and that, therefore, undue experimentation is required to search for other examples of cell lines, citing *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361 (CAFC 1997). At issue in *Genentech* was whether the specification described how to make hGH using cleavable fusion expression. The court found that undue experimentation was required because the specification did not describe any specific starting material or any of the reaction conditions for the steps needed to produce hGH. *Id.* at 1365-66. Unlike the specification at issue in *Genentech*, the present specification teaches antibodies that can be utilized to

establish the presence or absence of MHC antigen expression. "[T]he enablement requirement is met if the description enables any mode of making and using the invention." *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991). Furthermore, "representative samples are not required by the statute and are not an end in themselves." *Amgen, Inc., v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 quoting In re Robins, 429 F.2d 452, 456-7 (CCPA 1970). Accordingly, since the specification provides a mode of practicing the invention, another species of a cell line lacking MHC-I and MHC-II antigens in addition to the K562 cell line is not required.

In this regard, the Examiner again contends that the art reports that the SK-MEL-33 cell line and the cell lines of Ferrone et al. and Wang et al. do not lack both MHC-I and MHC-II. (NOTE: The Examiner's characterization of Ferrone et al. contradicts its characterization of Ferrone et al. with respect to the obviousness rejections.) This can be explained by differences in subclones. Also, this does not detract from the other examples of cell lines, which lack MHC-I and MHC-II expression, provided by Appellants.

On another note, the Examiner contends that the claims encompass and the specification exemplifies melanoma cells, which the art reportedly teaches require the presence of animal serum, while the claims are directed to the use of defined medium, which the specification defines as serum-free at page 14, line 26. Appellants point out that defined medium is only recited in dependent claims (see, e.g., claims 6, 9, 26 and 27). Furthermore, as taught in the instant specification at, for example, page 5, lines 18-19, the ability of the universal bystander to grow in defined, i.e., serum-free, medium is preferred -- not required. In response to the Examiner's contention regarding melanoma cells, Appellants point out that melanoma cells can be "weaned" of their requirement for animal serum by gradually reducing the amount of serum in the growth medium. For example, it is a matter of routine to reduce gradually the amount of serum in cell growth medium from 10% to 5% to 2.5%, until serum is not longer required.

Discussion of Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected all of the pending claims under Section 112, second paragraph, as allegedly indefinite. The Examiner should be reversed for the reasons set forth below.

The Examiner clearly understands that Appellants' use of the term "naturally" to describe the lack of MHC-I and MHC-II antigens on the universal bystander cell line encompasses a cell line that lacks MHC-I and MHC-II antigens due to a naturally occurring mutation, such as a cancerous mutation. However, the Examiner contends that use of the term "naturally" to encompass such a cell line is contrary to the ordinary meaning of the term, citing *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 U.S.P.Q.2d 1029, 1033 (Fed. Cir. 1999), and arguing that, when a cell mutates, it changes from its natural state.

At issue in *Process Control* was whether a term, recited in two different clauses of a single claim, should be construed to have the same meaning in both clauses. The Federal Circuit found that the claim language was "susceptible to only one meaning," based on "the language of the claim itself." *Id.* at 1356. According to the Federal Circuit, the claim language was not susceptible to two different constructions. *Id.* The Federal Circuit further found that the written description did not clearly redefine the disputed claim term so as to put a reasonable competitor or one skilled in the art on notice that the patentee intended to give the claim term a meaning contrary to its ordinary meaning. *Id.* at 1357.

Like *Process Control*, the present specification does not redefine the term "naturally" contrary to its ordinary meaning. The specification makes it clear that "naturally" is distinguished from "modified." See, for example, the specification at page 5, lines 3-6, where the universal bystander cell line is described as a human cell line, which either "naturally lacks" MHC-I antigens and MHC-II antigens, or is "modified" so that it lacks MHC-I antigens and MHC-II antigens. What is meant by "modified" is evidenced in the specification at, for example, page 7, lines 12-14, wherein it is stated that cells that lack MHC-I antigens can be achieved by interfering with the expression and/or transport of the α chain, whereas cells that lack MHC-II antigens can be achieved by interfering with the expression and/or transport of the α and β chains. Thus, a cell line that has been modified so that it lacks MHC-I and MHC-II antigens is one that lacks MHC-I and MHC-II antigens

without manipulation by man, i.e., it never had MHC-I and MHC-II antigens or, as a result of the effects of nature, it came to lack MHC-I and MHC-II antigens. This is supported by the Examiner's reference to a standard English dictionary as evidencing that the term "naturally" means "by nature, inherently," "without a doubt," and "present or produced by nature" (see Office Action dated April 10, 2003, at page 3, third full paragraph) and the Examiner's acknowledgement that "naturally" encompasses cells, which have lost the capacity to express MHC antigens as a result of naturally occurring mutations, as supported by the references previously provided by Appellants (see Office Action dated April 10, 2003, at page 4, first full paragraph).

Furthermore, like *Process Control*, the use of the term "naturally" in the claims is not susceptible to more than one meaning. For the Examiner to characterize the loss of MHC antigen expression due to a cancerous mutation as not "naturally" occurring (see the top of page 5 of the Office Action dated April 10, 2003) is directly contrary to the evidence of record, including the evidence entered into the record by the Examiner, herself, by way of the Office Action dated April 10, 2003. This is tantamount to saying that mutations, including cancerous mutations, do not occur naturally, and that every person, who has cancer, has cancer because his/her body was modified, or manipulated by man, in some way to cause the cancer. Appellants maintain that this is the only and, hence, ill-founded basis upon which the Examiner can continue to maintain a rejection for alleged indefiniteness.

The rejection of claim 2 as allegedly indefinite with respect to whether or not receptors for EBV are required to be absent is believed to be moot in view of the amendment of the claim. Claim 2 was amended to recite lowercase Roman numerals to clarify what is required.

Discussion of Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 5, 7, 17, 20, 22, 28, 40, 41, 44, 45, 50 and 52 under Section 103 as obvious in view of and, therefore, unpatentable over Dranoff et al., in view of Ferrone et al., as evidenced by Thomas et al. The Examiner should be reversed for the reasons set forth below.

Dranoff et al. does not teach or suggest a universal bystander cell line as taught by the present invention. Dranoff et al. also does not teach or suggest a composition comprising a universal bystander cell line, a method of making a universal bystander cell line, and a method of stimulating an immune response to a cancer in a human patient by administering the composition comprising a universal bystander cell line. Dranoff et al. does not appreciate the importance of using a cell line that naturally lacks MHC-I and MHC-II as taught by the present invention.

The Examiner admits that it is unclear whether the B16 melanoma disclosed by Dranoff et al. expresses MHC-I or MHC-II. The Examiner relies on Ferrone et al. as disclosing that various percentages of primary melanoma, metastatic melanoma, and melanoma cell lines lack MHC-I and normally lack MHC-II. The Examiner concludes that it would have been obvious to modify the methods of Dranoff et al. by substituting the B16 melanoma with melanoma cells that lack MHC-I and MHC-II as disclosed by Ferrone et al. with a reasonable likelihood of success. While admittedly not relying on Thomas et al., the Examiner attempts to bolster her reliance on the combined disclosure of Dranoff et al. and Ferrone et al. by pointing to Thomas et al. as disclosing that B78H1, a variant cell line of the B16 melanoma disclosed by Dranoff et al., lacks MHC-I. Thomas et al., however, teaches that the expression, i.e., the presence, of an allogeneic MHC molecule by a vaccine cell can actually enhance the induction of systemic antitumor immunity (see abstract). Such a disclosure teaches away from the use of a cell line that lacks MHC expression as taught by the present invention.

What the Examiner clearly fails to appreciate is that there is no teaching or suggestion in Ferrone et al. (alone or in further combination with Thomas et al.) to modify the alleged teachings of Dranoff et al. in the manner proposed by the Examiner. Therefore, one of ordinary skill in the art would not have been motivated to modify the alleged teachings of Dranoff et al. so as to arrive at the present invention, particularly in view of Thomas et al. In order to establish an obviousness rejection under Section 103(a), based on a combination of the prior art, the Examiner must show some motivation, suggestion, or teaching to make the specific combination claimed by the Appellants. *In re Kotzab*, 217 F.3d 1365 (Fed. Cir 2000), referring to *In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998). Furthermore, the Examiner must "cast the mind back to the time of the invention, to consider the thinking of

one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *Id.* referring to *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

The Examiner fails to point to any motivation or suggestion, either in the prior art or in the then-accepted wisdom in the field, to combine the references. According to the Examiner, "the references are combined to show that one of skilled in the art knows modifying tumor cells with GM-CSF would enhance anti-tumor immunity, and there is motivation to modify different types of tumor cells with GM-CSF, and one line of tumor cells modified may actually lacks both MHC-I and MHC-II." Office Action, pp. 9-10. Yet, the combination of references does not show that one of ordinary skill in the art would have known that modifying tumor cells with GM-CSF would have enhanced anti-tumor immunity for the reason set forth above. "The Examiner can satisfy the burden of showing obviousness of the combination 'only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teaching of the references.'" *In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) *quoting In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). Since the Examiner fails to provide the "objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teaching of the references," a *prima facie* case of obviousness cannot be established. In light of the foregoing, Appellants respectfully request withdrawal of this rejection.

The Examiner has rejected claims 1, 5, 7, 11, 17, 20, 22-24, 28, 40, 41, 44, 45, 50 and 52 stand rejected under Section 103 as obvious in view of and, therefore, unpatentable over Dranoff et al., in view of Ferrone et al., in further view of Shepard et al. or Polack et al. The Examiner should be reversed for the reasons set forth below.

As indicated above, Dranoff et al. does not teach or suggest a universal bystander cell line as taught by the present invention. Dranoff et al. also does not teach or suggest a composition comprising a universal bystander cell line, a method of making a universal bystander cell line, and a method of stimulating an immune response to a cancer in a human patient by administering the composition comprising a universal bystander cell line. Dranoff et al. does not appreciate the importance of using a cell line that naturally lacks MHC-I and MHC-II as taught by the present invention. Ferrone et al. does not cure the deficiencies of Dranoff et al. for the reasons set forth above. The fact that Shepard et al. or Polack et al. may

disclose the use of hygromycin resistance as a selectable marker is of no import then. Neither Shepard et al. nor Polack et al. cures the deficiencies of Dranoff et al. and Ferrone et al.

Therefore, the claimed invention cannot be said to be obvious in view of the cited references. Accordingly, the Examiner should be reversed.

The Examiner relies on *In re Keller* and *In re Merck* in support of her contention that Appellants are not addressing the cited references in combination. Appellants, however, adamantly maintain that they have, in fact, argued against the combination of cited references and have argued why the secondary references do not cure the deficiencies of the primary references. In this regard, Appellants point out that their approach differs from the approaches of the cited cases. In *Keller* an affidavit was submitted from an expert that attacked only one reference, not the combination of two references. In the case at hand, Appellants have addressed all of the references. In *Merck* the appellant tried to argue that one of the references taught away from the invention where the rejection was based on a combination of references. Here again, the case at hand is distinguishable from *Merck* inasmuch as Appellants have addressed all of the references.

Discussion of Obviousness-Type Double-Patenting Rejection

The Examiner has rejected claims 1-14, 17-28, 40-47 and 50-53 under the judicially created doctrine of obviousness-type double-patenting as unpatentable over claims 1-21 of U.S. Pat. No. 6,464,973. Upon an indication of allowable subject matter, Appellants will submit a terminal disclaimer, which will render this rejection moot.

Conclusion

For the above reasons, the Board is respectfully requested to reverse the Examiner.

Respectfully submitted,

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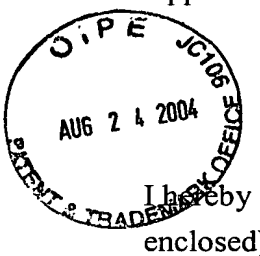
Date: August 20, 2004

In re Appln. of Levitsky et al.
Application No. 09/992,443



CERTIFICATE OF MAILING

I hereby certify that this document (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: August 20, 2004

Angelica Diaz
Signature

ANGELICA DIAZ
Typed or Printed Name

APPENDIX

1. (Previously amended) A universal bystander human cell line, which:

(i) is a human cell line,

(ii) naturally lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens, and

(iii) is modified by introduction of a nucleic acid molecule comprising a nucleic acid sequence encoding granulocyte macrophage-colony stimulating factor (GM-CSF) operably linked to a promoter,

wherein said universal bystander cell line expresses about 500 ng or greater GM-CSF/10^6 cells/24 hours.

2. (Previously amended) The universal bystander cell line of claim 1, wherein said human cell line is characterized by the absence of (i) B-lymphocyte markers of immunoglobulin, (ii) an Epstein-Barr virus (EBV) genome and an associated nuclear antigen, and (iii) receptors for EBV.

3. (Original) The universal bystander cell line of claim 1, wherein said human cell line is derived from a blast crisis of chronic myeloid leukemia.

4. (Original) The universal bystander cell line of claim 1, wherein said human cell line is K562.

5. (Previously amended) The universal bystander cell line of claim 1, which expresses about 1,000 ng or greater GM-CSF/10^6 cells/24 hours.

6. (Original) The universal bystander cell line of claim 1, which grows in defined medium.

7. (Original) The universal bystander cell line of claim 1, wherein said promoter is a cytomegalovirus promoter.

8. (Previously amended) The universal bystander cell line of claim 4, which expresses about 1,000 ng or greater GM-CSF/10^6 cells/24 hours.

9. (Original) The universal bystander cell line of claim 4, which grows in defined medium.

10. (Original) The universal bystander cell line of claim 4, wherein said promoter is a cytomegalovirus promoter.

11. (Previously amended) The universal bystander cell line of claim 1, wherein said nucleic acid molecule further comprises a nucleic acid sequence encoding hygromycin resistance operably linked to a promoter and said universal bystander cell line is selected by growth in a culture medium comprising about 400 μg/ml or greater hygromycin.

12. (Previously amended) The universal bystander cell line of claim 11, wherein said universal bystander cell line is selected by growth in a culture medium comprising about 1,000 μg/ml or greater hygromycin.

13. (Previously amended) The universal bystander cell line of claim 4, wherein said nucleic acid molecule further comprises a nucleic acid sequence encoding hygromycin resistance operably linked to a promoter and said universal bystander cell line is selected by growth in a culture medium comprising about 400 μg/ml or greater hygromycin.

14. (Previously amended) The universal bystander cell line of claim 13, wherein said universal bystander cell line is selected by growth in a culture medium comprising about 1,000 μg/ml or greater hygromycin.

15. - 16. (Canceled)

17. (Original) A composition comprising the universal bystander cell line of claim 1 and a cancer antigen.

18. (Original) A composition comprising the universal bystander cell line of claim 2 and a cancer antigen.

19. (Original) A composition comprising the universal bystander cell line of claim 4 and a cancer antigen.

20. (Original) A composition comprising the universal bystander cell line of claim 5 and a cancer antigen.

21. (Original) A composition comprising the universal bystander cell line of claim 8 and a cancer antigen.

22. (Previously amended) A method of making a universal GM-CSF-expressing bystander cell line, which method comprises:

(i) obtaining a human cell line that lacks MHC-I antigens and MHC-II antigens;

(ii) modifying said human cell line by introducing into said human cell line a nucleic acid molecule comprising a nucleic acid sequence encoding GM-CSF operably linked to a promoter and a nucleic acid sequence encoding a selectable marker operably linked to a promoter; and

(iii) using the selectable marker to isolate cells that produce about 500 ng or greater of said GM-CSF/10^6 cells/24 hours.

23. (Original) The method of claim 22, wherein said selectable marker is hygromycin resistance.

24. (Previously amended) The method of claim 23, wherein the modified human cell line is cultured in culture medium comprising about 400 μg or greater hygromycin/ml culture medium.

25. (Previously amended) The method of claim 24, wherein the modified human cell line is subsequently cultured in culture medium comprising about 1,000 μg or greater hygromycin/ml culture medium.

26. (Original) The method of claim 24, wherein said culture medium is defined.

27. (Original) The method of claim 25, wherein said culture medium is defined.

28. (Original) The method of claim 22, wherein the promoter to which the nucleic acid sequence encoding GM-CSF is operably linked is a cytomegalovirus promoter.

29. – 39. (Canceled)

40. (Original) A method of stimulating an immune response to a cancer in a human patient, which method comprises administering to said patient the composition of claim 17, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated,

whereupon administration of said composition, an immune response to said cancer is stimulated.

41. (Original) The method of claim 40, wherein said cancer antigen is a cell of said cancer.

42. (Original) A method of stimulating an immune response to a cancer in a human patient, which method comprises administering to said patient the composition of claim 19, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated,

whereupon administration of said composition, an immune response to said cancer is stimulated.

43. (Original) The method of claim 42, wherein said cancer antigen is a cell of said cancer.

44. (Original) A method of stimulating an immune response to a cancer in a human patient, which method comprises administering to said patient the composition of claim 20, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated,

whereupon administration of said composition, an immune response to said cancer is stimulated.

45. (Original) The method of claim 44, wherein said cancer antigen is a cell of said cancer.

46. (Original) A method of stimulating an immune response to a cancer in a human patient, which method comprises administering to said patient the composition of claim 21, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated,

whereupon administration of said composition, an immune response to said cancer is stimulated.

47. (Original) The method of claim 46, wherein said cancer antigen is a cell of said cancer.

48. - 49. (Canceled)

50. (Original) In a method of cancer immunotherapy, the improvement comprising administering to a human patient having a cancer the composition of claim 17, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated.

51. (Original) In a method of cancer immunotherapy, the improvement comprising administering to a human patient having a cancer the composition of claim 19, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated.

52. (Original) In a method of cancer immunotherapy, the improvement comprising administering to a human patient having a cancer the composition of claim 20, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated.

53. (Original) In a method of cancer immunotherapy, the improvement comprising administering to a human patient having a cancer the composition of claim 21, wherein said cancer antigen is an antigen of said cancer and wherein said composition is irradiated.